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New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey

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Aims The prognostic significance of atrial fibrillation (AF) in hospitalized patients with heart failure (HF) remains poorly understood. To evaluate in what way AF and its different modes of presentation affect the in-hospital mortality in patients admitted with HF.

Methods and results The EuroHeart Failure Survey was conducted to ascertain how hospitalized HF patients are managed in Europe. The survey enrolled patients over a 6-week period in 115 hospitals from 24 countries. For this analysis, patients were categorized into three groups according to the type of AF, previous AF (patients known to have had AF prior to admission), new-onset AF (no previous AF with AF diagnosed during hospitalization), and no AF (no previous AF and no AF during hospitalization). Clinical variables, duration of hospitalization, and in-hospital survival status were assessed and compared among groups. Of the 10 701 patients included in the survey; 6027 (57%) had no AF, 3673 (34%) had previous AF, and 1001 (9%) had new-onset AF. Patients with new-onset AF had a longer stay in the intensive care unit (ICU) when compared with previous AF and no AF patients (mean 2.6 ± 5.3, 1.2 ± 3.5, and 1.5 ± 4.1 days, respectively; $P < 0.001$). In-hospital mortality was higher among patients with new-onset AF when compared with previous AF or no AF patients (12, 7, and 7% respectively; $P < 0.001$). After adjusting for multiple clinical variables, new-onset AF (not previous AF) was an independent predictor of in-hospital mortality (odds ratio 1.53, 95% CI 1.1–2.0).

Conclusion In hospitalized patients with HF, new-onset AF is an independent predictor of in-hospital mortality and a longer ICU and hospital stay.

Keywords Atrial fibrillation • Recent onset • Heart failure • Mortality • Hospitalization

Introduction

The prevalence of atrial fibrillation (AF) and heart failure (HF) is increasing due, at least in part, to the increasing proportion of the population that is aged >60.[1,2] They share common predisposing factors and therefore commonly co-exist.[3] Many reports have addressed the issue of whether AF is a marker of worse prognosis in patients suffering from HF and arrived at contradicting conclusions.[4–9] However, recently published sub-analyses of large randomized controlled trials performed in patients with HF, and epidemiological studies suggest that either prevalent and/or incident AF is associated with a worse long-term outcome.[2,10–14]

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Hospitalization is a common event in patients with HF; it occurs more frequently in advanced stages of the disease, it is a marker of worse prognosis, and it is in this setting that most deaths due to progressive HF occur. Nevertheless, there are few data on how AF affects the in-hospital course and prognosis of patients with HF. With this purpose in mind, the EuroHeart Failure survey database was analysed in order to establish, in a 'real-world' population of hospitalized HF patients, how AF affects the length of hospital stay and in-hospital survival.

Methods

The EuroHeart Failure Survey was the second in a series of surveys that were conducted under the umbrella of the EuroHeart Survey Program, which aimed to investigate the implementation of treatment guidelines in clinical practice. The design details of the EuroHeart Failure Survey, which was undertaken between March 2000 and May 2001, were published previously.[15] In short, 45 933 consecutive discharges and deaths in the departments of cardiology, cardiovascular surgery, general internal medicine, and geriatrics were screened over a 6-week period. The survey included 115 hospitals from 24 ESC member countries, including community hospitals and regional university centres. Patients were enrolled if they fulfilled at least one of the following criteria:

- a clinical diagnosis of HF during the admission;
- a diagnosis of HF recorded at any time in the last 3 years;
- administration of a loop diuretic for any reason other than renal failure withing 24 h of death or discharge;
- pharmacological treatment for HF or ventricular dysfunction within 24 of death or discharge.

For the purpose of this analysis, patients were categorized according to the type of AF in the following groups: (i) previous AF: those patients who were known to have had AF prior to hospital admission (irrespective of whether it was paroxysmal, persistent or permanent), (ii) new-onset AF: patients with no prior history of AF and who were diagnosed as having AF during hospitalization, and (iii) no AF: patients with no prior AF and not suffering AF during hospitalization. Clinical variables, treatment, length of stay in the coronary care unit/intensive care unit (CCU/ICU), length of hospitalization, hospital survival, and cause of death were analysed according to the type of AF.

Statistical analysis

Continuous variables are described as mean values with their corresponding standard deviations or as median values and corresponding 25th and 75th percentiles. Dichotomous variables are reported as absolute numbers and percentages. To evaluate the differences in clinical characteristics, pharmacological treatment, length of ICU and hospital stay, and in-hospital survival between patients according to the type of AF, χ^2 tests for more than two groups were applied. ANOVA test was used for comparison of continuous variables. Multivariable logistic regression analysis was applied to study the relationship between the type of AF and all-cause in-hospital mortality and a long length of ICU (>75th percentile = 2 days) and hospital stay (>75th percentile = 13 days). Clinically relevant variables such as type of AF, age, gender, hypertension, diabetes, ischaemic heart disease, valvular heart disease, prior renal insufficiency, prior stroke, rapid AF (defined in the protocol as >120 b.p.m.), moderate or severe left atrial dilatation (as assessed by the investigators), and the presence of left ventricular (LV) dysfunction [ejection fraction (EF) $\leq$ 50%] were forced into the regression model where no AF was used as the reference group. We report the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All calculations were performed using SPSS 14.0 software package. For all tests, $P \leq 0.05$ or less (two-sided) was considered as statistically significant.

Results

Of the 10701 patients included in the survey, 6027 (57%) had no AF prior to or during hospitalization (no AF group), 3673 (34%) were known to have had AF prior to admission (previous AF group), and 1001 (9%) had no AF before admission but were reported to have AF during admission (new-onset AF group) (*Table 1*). Patients with no AF were younger than patients with AF (irrespective of type) (70 $\pm$ 13 vs. 73 $\pm$ 12; $P < 0.001$). The proportion of patients with a reduced LVEF was similar between groups but more patients with prior AF or new-onset AF had moderate or severe left atrial dilatation as compared to no AF patients (28, 17, and 13% respectively; $P < 0.001$). Rapid AF was more frequent in the new-onset AF group when compared with the previous AF group (77 vs. 27%; $P < 0.001$). Patients with new-onset AF were more frequently treated in-hospital with anti-arrhythmic drugs than those with previous AF or no AF (32, 22, and 7%, respectively; $P < 0.001$). Digitalis and anticoagulation use was higher in patients with AF irrespective of the type.

Duration of intensive care unit stay and hospitalization

The mean length of stay in the ICU for the entire population was 1.5 $\pm$ 4.1 days. Patients with new-onset AF had a significantly longer stay in the ICU when compared with previous AF and no AF patients (2.6 $\pm$ 5.3, 1.2 $\pm$ 3.5, and 1.5 $\pm$ 4.1 days respectively; $P < 0.001$) (*Table 2*). When adjusting for multiple clinical variables, new-onset AF (OR 1.45, 95% CI 1.2–1.8) and rapid AF (OR 1.84, 95% CI 1.5–2.1) were independent predictors of a longer stay in the ICU (*Figure 1*). However, previous AF was not predictive of a longer ICU stay.

The mean amount of days hospitalized for the entire population was 12 $\pm$ 12. Patients with new-onset AF were admitted longer than those with previous AF and no AF (14 $\pm$ 12, 13 $\pm$ 12, and 12 $\pm$ 12 days, respectively; $P <$ 0.001) (*Table 2*). After adjusting for multiple clinical variables, new-onset AF (OR 1.46, 95% CI 1.2–1.7) was an independent predictor of a longer hospitalization (*Figure 2*).

In-hospital mortality

There were 791 deaths (7%) during admission. In-hospital mortality was higher among patients with new-onset AF when compared with previous or no AF patients (12, 7, and 7%, respectively; $P < 0.001$). New-onset AF and rapid AF (but not previous AF or the presence of AF irrespective of the type) were predictors of mortality in the univariate analysis. When introducing these variables in a multiple logistic regression model, new-onset AF (OR 1.53, 95% CI 1.1–2.0) remained an independent predictor of in-hospital mortality (*Figure 3*). Left atrial dilatation was also independently associated to a worse prognosis (OR 1.31, 95% CI

Table 1 Clinical characteristics and pharmacological treatment of patients enrolled in the EuroHeart Failure Survey by type of atrial fibrillation (n = 10 701)

	No AF (n = 6027)	Previous AF (n = 3673)	New onset AF (n = 1001)	P-value[a]
Mean age in years (SD)	70 (13)	73 (12)	73 (12)	<0.001
Male	3260 (54%)	1859 (51%)	523 (52%)	0.005
Clinical characteristics				
Rapid AF (>120 beats/min)	0 (0%)	1000 (27%)	768 (77%)	<0.001
Ischaemic heart disease	3921 (65%)	2070 (56%)	563 (56%)	<0.001
Acute coronary syndromes	1192 (30%)	363 (18%)	212 (38%)	<0.001
Prior revascularization	935 (16%)	423 (12%)	98 (10%)	<0.001
EF known	3739 (54%)	2484 (36%)	672 (10%)	<0.001
Mean EF[b] (SD)	0.42 (0.15)	0.44 (0.16)	0.45 (0.15)	<0.001
LVSD (EF ≤ 45%)[b]	2482 (66%)	1570 (63%)	419 (62%)	0.013
Moderate/severe LA dilatation	788 (13%)	1023 (28%)	167 (17%)	<0.001
Not reported	3269 (54%)	1702 (46%)	507 (51%)	<0.001
Valvular heart disease	649 (11%)	688 (19%)	142 (14%)	<0.001
Prior stroke	794 (13%)	665 (18%)	125 (13%)	<0.001
Prior renal insufficiency	647 (11%)	477 (13%)	83 (8%)	<0.001
Diabetes	1715 (29%)	944 (26%)	221 (22%)	<0.001
Hypertension	3202 (53%)	1973 (54%)	504 (50%)	0.165
Pulmonary disease	1830 (30%)	1244 (34%)	303 (30%)	0.001
BMI (mean, SD)	27.1 (5.2)	26.8 (5.2)	26.8 (5.2)	0.056
Medical treatment during hospital admission				
Anti-arrhythmic drugs	437 (7%)	822 (22%)	315 (32%)	<0.001
Antiplatelets	3461 (57%)	1604 (44%)	528 (53%)	<0.001
Anticoagulants	1996 (33%)	1999 (54%)	567 (57%)	<0.001
ACE-I or ARB	3933 (65%)	2445 (67%)	615 (61%)	0.01
Beta-blockers	2385 (40%)	1199 (33%)	360 (36%)	<0.001
Digoxin	1236 (21%)	2068 (56%)	521 (52%)	<0.001
Diuretics	5119 (85%)	3302 (90%)	876 (88%)	<0.001

ACE-I, angiotensin-converting enzyme-inhibitors; ARB, angiotensin II receptor blockers; AF, atrial fibrillation; EF, ejection fraction; LA, left atrial.
[a]χ^2 for more than two groups for categorical variables and ANOVA for continuous variables.
[b]Based on those patients in whom EF was known.

Table 2 In-hospital evolution

	No AF (n = 6027)	Previous AF (n = 3673)	New-onset AF (n = 1001)	P-value[a]
Days in ICU or CCU				
Mean (SD)	1.5 (4.1)	1.2 (3.5)	2.6 (5.3)	<0.001
Median (IQR)	0 (0–1)	0 (0–0)	0 (0–3)	<0.001
Days hospitalized				
Mean (SD)	12 (12)	13 (12)	14 (12)	<0.001
Median (IQR)	9 (5–15)	9 (6–16)	11 (7–17)	<0.001
In-hospital mortality	419 (7%)	249 (7%)	123 (12%)	<0.001

[a]χ^2 for more than two groups for categorical variables and ANOVA for continuous variables.

1.1–1.4) and rapid AF showed a tendency towards an increased mortality. However, the presence of previous AF did not predict the in-hospital survival.

Mode of death

Overall, the predominant causes of death were worsening HF (32%) followed by pulmonary oedema (24%) and other

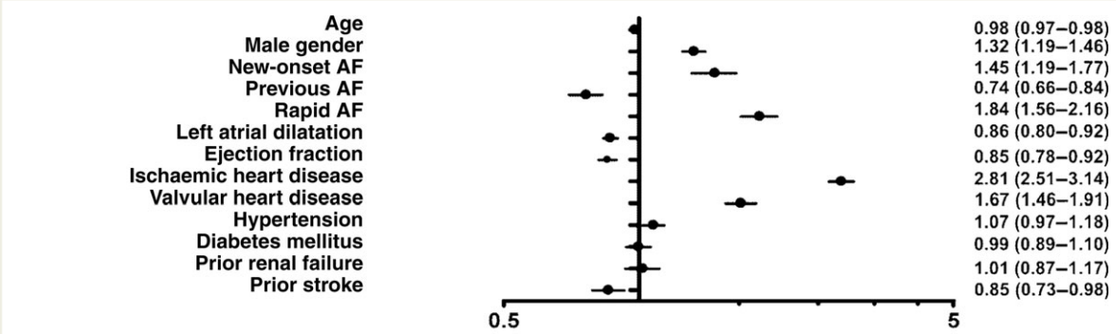

Figure 1 Independent predictors of length of stay in the CCU–ICU.

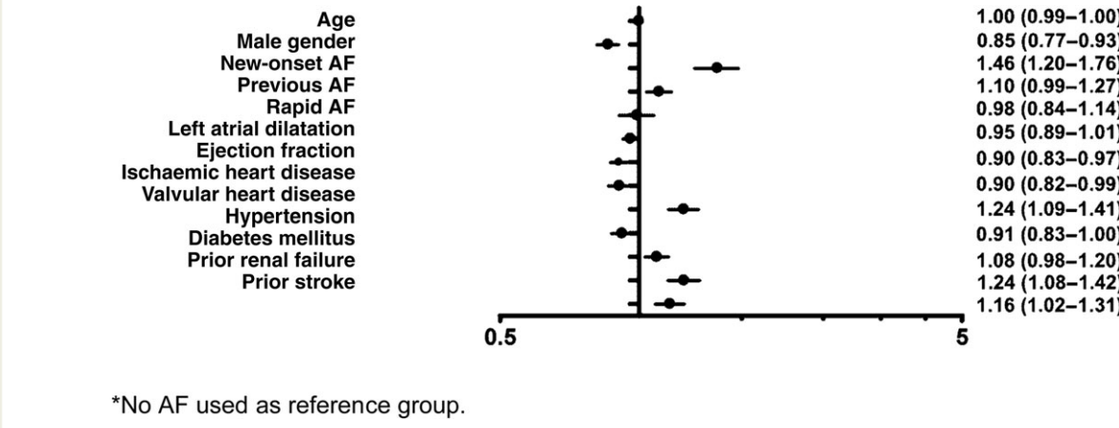

Figure 2 Independent predictors of length of hospitalization.

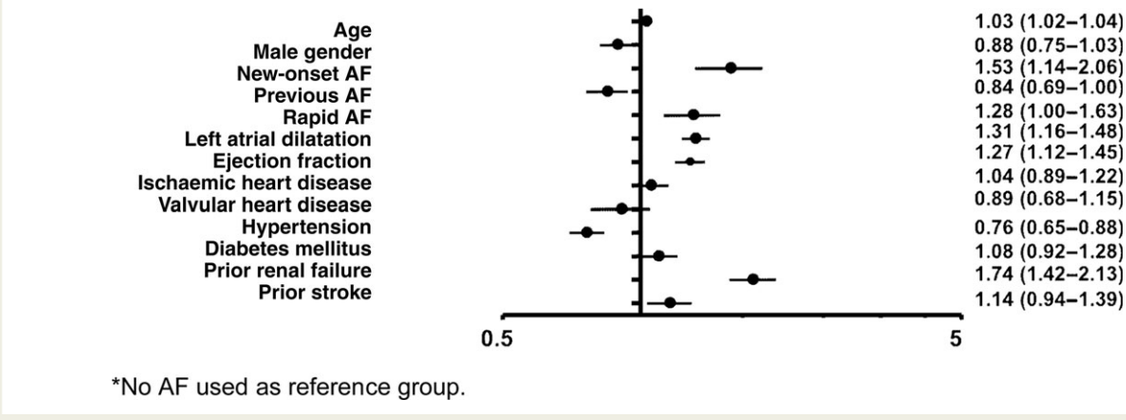

Figure 3 Independent predictors of in-hospital mortality.

Table 3 Mode of death by type of atrial fibrillation[a]

	No AF (n = 419)	Previous AF (n = 249)	New-onset AF (n = 123)	P-value[b]
Worsening heart failure	141 (34%)	71 (29%)	42 (34%)	<0.001
Pulmonary oedema	99 (24%)	58 (23%)	34 (28%)	<0.001
Stroke	17 (4%)	27 (11%)	8 (7%)	<0.001
Other cardiovascular cause	79 (19%)	35 (14%)	27 (22%)	<0.001
Non-cardiovascular cause	71 (17%)	40 (16%)	25 (20%)	<0.001

[a]Data collectors could choose more than one cause.
[b]χ^2 for more than two groups for categorical variables and ANOVA for continuous variables.

cardiovascular causes (18%). No differences were observed regarding causes of death between the different groups (*Table 3*).

Discussion

This study shows that new-onset AF is common in patients hospitalized with HF, occurring in 9% of admissions, and that it is associated with a higher in-hospital mortality, conferring a 53% increased risk independent of other relevant clinical variables such as age, sex, LVEF, and renal function. In patients with new-onset AF, both hospital and ICU stays were longer, even after adjusting for other clinically relevant variables. Our findings also show that having had AF prior to admission did not affect hospital survival or length of stay.

Middlekauf *et al.*[4] reported, in a cohort of 390 patients, that 1-year mortality was higher in patients with HF if they had AF but a report from the Vasodilator in Heart Failure Trials (V-HeFT) suggested that AF was not associated with a worse survival.[8] Subsequently, Stevenson *et al.*[9] compared the prognosis of patients with and without AF evaluated for heart transplantation between 1985 and 1989 with those evaluated between 1990 and 1993. They reported that AF was associated with a worse outcome only during the first time period and suggested that changes in treatment, such as the use of ACE-inhibitors and a reduction in the use of class I anti-arrhythmic drugs, might account for this observation. In a subgroup of 409 patients in the PRIMIE-II study, Crijns *et al.*[5] showed that patients with AF had a higher mortality than patients in sinus rhythm but this could be accounted for by differences in age, disease severity, and co-morbidity. Neither the presence of AF nor the development of AF was independent predictor of mortality during long-term follow-up. A retrospective analysis of the SOLVD trials showed that in a much larger cohort of 6517 patients (419 with AF) AF was independently associated with a 34% increase in overall mortality after a mean follow-up of 33 months.[6]

Other trials also assessed the impact of new-onset AF in this patient population and results are more consistent in establishing the role of new-onset AF as a marker of poor outcome.[7,16–19] In a *post hoc* analysis of the COMET trial, the authors report that baseline AF did not independently predict mortality; however, onset of AF during the study was independently associated with a worse survival during follow-up (RR 1.9).[12] The CHARM studies showed that new-onset AF was an independent predictor of adverse outcome in patients with depressed or preserved LV systolic function (OR 2.57 in preserved and 1.85 with reduced LVEF).[11] In agreement with these findings, the DIG investigators reported that the development of new-onset supraventricular arrhythmias was independently associated with a reduced survival during the follow-up (HR = 2.45).[10]

A recent report from the Framingham Heart Study evaluated the time relation between the onset of HF and AF.[13] It showed that patients with established HF who later on developed AF carried an increased risk of death (RR 1.6). Other observational studies performed in hospitalized HF patients show that the occurrence of AF is associated with a worse long-term prognosis.[7]

It is unclear whether chronic AF has an adverse impact on prognosis in patients with well-established HF who receive the high quality of management expected in clinical trial centres. However, new-onset AF appears to predict an adverse outcome during long-term follow-up.

Role of atrial fibrillation during heart failure hospitalization

Hospitalization is a turning point in the natural history of HF. Patients with chronic HF who require hospitalization have a worse prognosis and many will die during the first or a subsequent admission. Accordingly, it is important to understand the role that AF plays during this period. We showed in a broad population of patients hospitalized for or with HF that new-onset AF (but not prior AF) adversely affected hospital survival, despite the fact that patients with new-onset AF had an apparently lower risk profile than those with previous AF or no AF. Patients with new-onset AF were less likely to have renal dysfunction, diabetes, hypertension, or a previous stroke. Nonetheless, mortality among new-onset AF patients was twice as high as that of patients in the other groups. Pozzoli *et al.*[16] showed that the development of AF was associated with a sudden reduction in cardiac index, rise in filling pressures, and a worse prognosis shortly after its initiation, but this did not persist after longer follow-up. Therefore it is possible that increased mortality is due to the adverse consequences of new-onset AF on cardiac function. However, it is also possible that the cause of new-onset AF is also the reason for the increase in mortality, making AF a marker but not a mediator of mortality. The causes leading to death in the patients with new-onset AF were predominantly related to decompensated HF (*Table 3*). The mechanisms leading to mortality in recent-onset AF patients are probably different (predominantly haemodynamic) than

those in long standing forms of the arrhythmia (stroke, progressive remodelling, etc.). Furthermore, our study suggests that those HF patients who go on to develop persistent forms of AF are probably those who were able to survive the initial stages of the arrhythmia.

Study limitations

There are certain limitations regarding this study that should be considered when interpreting the results. This survey was not conducted with the purpose of evaluating the relation of AF occurrence and hospitalization prognosis. Consequently, relevant information regarding specific characteristics of AF and management of the arrhythmia during admission was not accounted for. It should also be noted that categorization according to the type of AF was retrospectively performed and thus subject to misclassification. However, studying large sample sizes and screening for consecutive patients provide protection against random and systematic error, respectively. Furthermore, clinical characteristics of the different groups seem to be representative of what would be expected; for example: the presence of left atrial dilation was higher in previous AF than in new-onset AF or no AF, prior stroke was more common in patients with AF than in no AF, antiarrhythmic drug therapy was more common in patients suffering from AF than those without it, etc.

Even though surveys attempt to make a realistic description of a certain clinical situation, it could be argued that a potential limitation of this study is the heterogeneity of the population included (patients were recruited from different departments and were HF was not always the primary diagnosis) that may not be completely representative of the HF population. However, it was not the objective of this survey to restrict the enrolment to the HF population usually included in clinical trials.

Our results suggest that the development of AF in hospitalized patients with HF is a relevant clinical event that should be adequately approached. Although it should be prospectively determined, measures aiming at preventing the occurrence of AF during admission and appropriate and expeditious treatment of these episodes seem warranted in order to improve the survival of hospitalized HF patients.

It should be borne in mind that in an important proportion of patients no echocardiogram was performed during or prior to the index admission; therefore, information regarding EF and left atrial dimension should be cautiously interpreted accordingly.

Conclusion

In hospitalized patients with HF, the occurrence of new-onset AF was associated with a longer stay in the ICU, a longer hospitalization, and higher in-hospital mortality independently from other relevant clinical variables.

Conflict of interest: none declared.

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CLINICAL VIGNETTE

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Non-compaction cardiomyopathy with low-gradient aortic valve stenosis

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A 73-year-old man presented to the emergency department with dyspnea of 2 days duration. Auscultation of the precordium was notable for a grade 2/6 systolic murmur. Echocardiography revealed a highly impaired left ventricular function and a calcified aortic valve stenosis with a mean pressure gradient of 25 mmHg and a valve area of 0.8 cm^2. Eye-catching was a thickened mid-ventricular and apical myocardium with a spongy appearance. On magnetic resonance imaging (MRI) multiple, prominent muscular trabeculations of the left ventricular myocardium (white arrows) with deep intertrabecular recesses were evident (Panel A, LV: left ventricle, LA: left atrium). These findings were consistent with non-compaction cardiomyopathy with accompanying low-gradient aortic valve stenosis. The patient underwent mechanical aortic valve replacement, during which the spongy left ventricular myocardium was visualized by video endoscopy (Panel B). The histological workup of an endomyocardial biopsy specimen showed irregular heart muscle fibres with vacuolar changes and large chromatin-dense nuclei as well as moderate interstitial fibrosis (Panel C, haematoxylin and eosin staining, magnification: original ×20). The patient made a full recovery and was discharged on heart failure medication and oral anticoagulation. Screening of first-degree relatives by MRI revealed left ventricular non-compaction with a preserved ejection fraction in the patient's asymptomatic son (Panel D, LV: left ventricle, LA: left atrium).